

Managerial Innovation in Hospitals: An Analysis of Adoption of Micro Costing

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Abstract:

The accounting information associated with clinical results is able to map the real cost efficiency in the clinical trial. The study analyzes explicitly the clinical trial carried out in 2017 by the "Bambin Gesù" Pediatric Hospital in Rome (Italy). The survey for the first time classifies the costs of a clinical trial on the use of micafungin in pediatric patients. The study provides an example of ways and items of expenses related to the clinical trial. The methodology used is applicable and can be used to compare future trials, thus identifying reference benchmarks. The study through practical application seeks to identify the correct method to avoid errors during the detection of clinical trials as evidenced by the study by Graves et al. (2002) through a proper application. The article also highlights the main cost items to be kept under control during the clinical trial phases. Moreover, given the incidence of candida in children, the study increases the literature on the administration and testing of specific drugs for treatment and therapy

Keywords: clinical trial; micro-costing approach; micafungin; pediatric

Introduction

Invasive candidiasis is a major cause of morbidity and mortality in intensive care healthcare settings and are largely associated with the use of invasive procedures and extensive use of new generation cephalosporins and other broad-spectrum antibiotics, essential for these delicate patients to survive. Therefore these infections are associated with technological and pharmaceutical progress in intensive medical care.

In neonates, the most severe risk factor for candidiasis is prematurity because the related functional insufficiency of the immune system and invasive procedures performed in the context of neonatal intensive care units. (Auriti, Falcone, et al., 2016). The incidence of the disease for newborns weighing less than 1000 g at birth is around 10% (Bochennek et al., 2015). Mortality among infected neonates is very high: in the case of gestational age less than 28 weeks and birth weight lower than 1000 g the mortality rate is between 40-50% of cases (Bochennek et al., 2015; Hope et al., 2010).

In children up to 18 years, the main risk factor for candidiasis infection is cancer (Hope et al., 2010). In addition to this, the disease occurs in the case of prolonged treatments that cause severe neutropenia, in patients undergoing induction therapy in the course of acute myeloid leukemia and non-Hodgkin's lymphoma, in patients who receive transplantation of bone marrow and are under myeloablative therapeutic regimens (Arrieta et al., 2011). An increased risk of invasive candidiasis is observed in children who are carriers of inherited immune disorders (Kawaguchi et al., 2009). For this evidence, invasive candidiasis is one of the significant causes of morbidity and mortality in neonatal and pediatric age (Kobayashi et al., 2015). Patients with *Candida* infections generally present a severe clinical picture, aggravated by low immunocompetent defences. For this reason, the medical staff is often forced to treat patients with invasive procedures, such as the using of external oxygen, central venous catheters, endotracheal tubes for mechanical ventilation, broad-spectrum antibiotics, high doses of corticosteroids (Nguyen et al., 2009). This situation may have a heavy economic impact on the economic management of healthcare companies. Usually, the days of hospitalization are prolonged for an average period of 21.1 days, attributable to the infection, which creates an average increase in hospital costs of \$ 39.331 per patient (Leroux et al., 2018).

Therapies to manage *Candida* infections vary substantially and the choice of the drug to start the therapy is currently based on the anatomic location of the infection, the patients' underlying disease and immune status, the specific species of *Candida* responsible for infection, the susceptibility of the *Candida species* to antifungal drugs and on the recommendations included in specific international guidelines.(Arrieta, Maddison, & Groll, 2011; Auriti, Falcone, et al., 2016).

In the last ten years, many significant changes have occurred in the management of candidiasis, particularly concerning the appropriate use of echinocandins (Benjamin 2016) and expanded-spectrum azoles for candidemia and other forms of invasive candidiasis. In 2016 the Infectious Disease Society of America (IDSA), published Updated guidelines (Peter G. Pappas, Carol A. Kauffman, David R. Andes, Cornelius J. Clancy, Kieren A. Marr, Luis Ostrosky-Zeichner, Annette C. Reboli, Mindy G. Schuster, Jose A. Vazquez, Thomas J. Walsh, Theoklis E. Zaoutis, and Jack D. Sobel Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America Clinical Infectious Diseases® 2016;62(4):e1–50) replacing previous versions. According to guidelines several drugs can be used in the treatment of invasive candidiasis in no neutropenic patients: medications belonging to the class of echinocandins, caspofungin, anidulafungin, and micafungin, and triazoles, which includes fluconazole, which may be administered intravenously or orally (Benjamin et al., 2004). Among echinocandins, micafungin shows to have high efficacy against *Candida*. Unlike other antifungals, micafungin is also able to destroy the intraluminal biofilm, that *Candida* frequently produces in central venous catheters, hindering its functioning and generating the persistence of the infection, despite the therapy (Nguyen, MHIME, & Ellis, 2009).

Although partially studied in the newborn, micafungin is frequently used in the treatment of neonatal invasive candidiasis. Micafungin has been approved for use in neonates in Europe but the literature reports deep uncertainty about the dosage in neonates. The drug should therefore not be recommended as the first choice in newborns.

Given the high incidence of invasive candidiasis in neonates and considering the unresolved questions on the use of micafungin in this population, at Bambino Gesù Children' Hospital in Rome we carried out a phase 2 study, to evaluate the plasma levels of high doses of micafungin and the optimal doses of the drug for infants and children up to 90 days of life, suffering from systemic candidiasis. Unlike other clinical trials conducted in our and other research Institutes, this study was completed with a careful evaluation of the costs, providing evidence on the economic impact generated by a clinical trial for the management of severely ill neonates with candidiasis.

Methodology

The study was authorized as "non-profit" in 2015 by AIFA and the OPBG Ethics Committee. The American pharmaceutical company Astellas (producer of the drug Mycamine), which had previously tried to promote a similar pharmacokinetic study unsuccessfully, asked OPBG to acquire the study data, in order to submit data to USFDA, to license in the United States the marketing and therapeutic use of micafungin in neonates and infants up four months of age. As a first step, we verified the feasibility of the transaction, which included the change in the type of clinical study, from a non-profit study to a study for registration and market purposes. This phase 2 study was conducted in the Department of Medical and Surgical Neonatology (Principal Investigator) and in the Laboratory of Metabolic Pathology (Co-Investigator) of Bambino Gesù Children's Hospital.

The Bambino Gesù Hospital ranks among those experienced and already active on *Candida* and use of micafungin, therefore, it is considered reliable in terms of collection and analysis of financial and non-financial information (Auriti, Piersigilli, et al., 2016). In the analysis conducted related to the micro costings (Frick, 2009) associated with the clinical results will be presented as foreseen for the first health trials. Very often, clinical trials also detect various errors in reporting results and errors in the reporting approach using the micro-costing method. The study tries to overcome the possible errors with a correct application (Graves, Walker, Raine, Hutchings, & Roberts, 2002). The flanking of qualitative analysis around the case guarantees the validity of what is expressed and analysis (Glaser & Strauss, 1967). External validity is possible because of the characteristics related to the document. The generalization of research results in similar contexts is possible through the analysis of the elements (Eisenhardt, 1989). The analysis and the treatment were conducted taking into consideration also reliability as the schola withers usually would need to do when talking about case studies. "Reliability" refers to the absence of random error, enabling subsequent researchers to arrive at the same insights if they conducted the study along the same steps again

(Denzin & Lincoln, 2002). Transparency and the possibility of replicating the research allow and guarantees this aspect and is also confirmed by the verification and authorization supervision of the Italian Drug Agency (AIFA).

Scenario and clinical trial

An agreement was signed between the Astellas company and the "Bambino Gesù" Children's Hospital in Rome, which provides for the involvement of 48 subjects. In neonates, to obtain an effective therapy using Mycamine drug doses up to 5 times those indicated are given without any support of Clinical Pharmacokinetic Studies adequate for the number of cases treated. Subjects received treatment for a total of 16 days on average. The average weight of patients at the beginning of the therapy was 2.86 kg, this information is relevant because it is related to the dosage of the drug and therefore, to the cost of the therapy. The average days of hospitalization per patient refer to the total period of stay in the hospital and are equal to 144 total days.

Results and discussion

The data necessary for the evaluation were selected, and the different types of costs were collected in quantification as required of the micro-costing approach (Frick, 2009). The Direct variable costs include the cost of therapy and study and analysis costs. The Direct fixed costs include the costs of the C.R.O. activity and general ethical committee referable to the clinical study in its entirety. The Variable indirect costs include ancillary health costs incurred to make patient stay possible.

The nature of the reported costs was found to be of two categories. Conventional costs derive from internal tariffs acquired, then actual costs derive from actually incurred, calculated on time.

The analysis of the actual costs (direct and indirect) incurred by the Hospital to carry out the Clinical Study and gather the results is composed as follows: Accessory healthcare costs are equal to 42%, the costs related to the activities carried out by the Ethics Committee are 19%, the costs of study and laboratory analysis are equal to 26%, and finally, the personnel costs are equal to 13%.

If these costs are differentiated by nature it is immediately evident that 60% refers to real costs while 40% refers to costs falling within the tariff in terms of recognition of the expense incurred by health institutions accredited by the regional health system.

The fixed direct costs are mainly formed by the activities related to the establishment of practices and ethics committee as defined in table 1.

Table 1 Direct fixed cost

Cost item	Description	Value €	% on the total
Cost C.R.O.	(Rate for services) Tariff C.R.O. for services and documentary activities related to the PK study based on market standards	189,360	88.99
Activity Cost Ethical Committee	(Rate per service) Possible cost for Studio «Profit»	16,000	7.52
Insurance Cost	(Cost per service) The cost incurred for Clinical Study	7,425	3.49
Total direct fixed costs		212,785	

The variable direct costs are mainly formed by the study and laboratory analysis which includes the involvement of two scholarship holders in the study, preparation and validation costs of the method, biologist activities on the first group of patients and the cost of the study fees as shown and quantified in table 2. The variable direct costs are also added to the costs of administering therapies formed by the costs for drugs and by the hours of the pharmacy for the management of the activity.

Table 2 Variable direct costs

Cost item	Description	Value €	% on the total
2 scholarship holders	(Personal cost x dedicated hours) 26 monthly payments + meal vouchers	31,900	7.32
Cost of preparation and validation of the analysis method on HPLC	The average cost of a Department Biologist for the study, development, and validation of the method experimentation of the dosage = 20 days. of work. Study of the project, data reporting, and participation in congresses = 25 days. of work.	18,851	4.33
Biologist activity 1st patient group	(Personal cost x no. Hours) The average cost of a biologist in the department for 16h and 25 'of processing times per patient (Dott.ssa Data Godfrey - Metabolic Pathology).	5,444	1.25
Cost of Studio "Fees"	(Service fee - Fees) Price list enhancement, including pharmacokinetic analysis, provided by "Ethics Committee" and validated by C.R.O. based on standard market rates.	235,949	54.16
Disposable drug cost	(material cost: unit drug cost x n. doses) The 50mg vial can only be used for the clinical study. In rare cases of the concomitance of therapy one vial was used for the doses of 2 patients.	134,176	30.80
Pharmacy	(personal cost x no. hours) The average cost of nurses and pharmacists for the preparation of the drug (€ 12), multiplied for the patient's therapy days.	9,341	2.14
Total variable direct costs		435,661	

The aforementioned costs are also joined by the variable indirect costs formed mainly by the accessory healthcare costs Table 3.

Table 3 variable indirect costs

Cost item	Description	Value €	% on the total
Material cost used in the ward during therapy	(material cost: consumption x bed x therapy day) The average cost of materials consumed per bed in the Neonatology Department multiplied by the days of patient therapy.	71,980	15.67
Cost of ward personnel during therapy	(personal cost x bed x therapy day) The average cost of the staff of the Neonatology Department per bed multiplied by patient therapy days.	293,309	63.85
Cost of activities carried out by the Cooperatives during the therapy	(cost of cooperatives x bed x therapy days) The average cost of Cooperative activities for the Neonatology Department for bed multiplied by the days of patient therapy.	42,272	9.20
General costs of the department incurred during the therapy	(indirect costs x bed x therapy days) Average Cost General Costs for the Neonatology Department for bed multiplied by patient therapy days.	31,140	6.78
Depreciation of machinery used in the treatment period	(depreciation x bed x therapy days) The average cost of amortization of the machinery of the Neonatology Dept. for bed multiplied by the days of patient therapy.	20,691	4.50
Total of variable indirect costs		459,393	

The most important fixed costs concern the fulfillment of the documentation relating to the technical specialty. The variable direct costs that must be taken into greater consideration are those relating to the pharmacological study and the costs for the drug itself. If, on the other hand, indirect variable costs are

considered, as is frequently reported in the literature, the higher costs are related to personnel (Biancone et al., 2019), which account for 63.85% of total indirect costs.

The total costs of the trial are € 1,107,838. The costs of the clinical trial for each patient, therefore, amount to € 23,080 and are made up of health care accessory costs for € 9,571, costs related to the ethics committee for € 4.443, study and laboratory analysis for € 6.086, therapy costs for € 2,990.

According to the analysis by (Arrieta et al., 2011) which considers 1,118 hospital admissions for candidiasis, children suffering from this disease have a time of hospitalization equal to 44.8 days against an average period of 23.7 days in case of absence. The value of direct and indirect costs for a patient with candidiasis is \$ 183,645 compared to a cost of \$ 91,379 for patients hospitalized but without candidemia (Leroux et al., 2018). This creates an increase in hospitalization days averaging 21.1 and costs of \$ 92,266. Therefore, the identification of an effective dosage and treatment would reduce hospital stay times increasing the effectiveness of the therapy reducing costs.

In the literature, different individual articles that identify the effects of the drug in new-borns consider a birth period between a few days and 24 weeks (Arrieta et al., 2011; Benjamin et al., 2006; Kobayashi et al., 2015; Makhoul, Sujov, Smolkin, Lusky, & Reichman, 2002; Maximova, Schillani, Simeone, Maestro, & Zanon, 2017; Santolaya et al., 2013; Queiroz-Telles et al., 2008) and reflect a level of administration up to 10 mg / kg / day.

Only two results concern the analysis and efficacy of micafungin in children under the age of one month (Auriti et al., 2016; Santolaya et al., 2013), in these cases the initial dose is set at 2 mg / kg / day with a possible increase up to 15 mg / kg / day in order to mitigate the risks deriving from overexposure to candidiasis (Schonfeld et al., 2008). The frequency of drug administration in these results is always daily.

In the trial conducted, therefore, the suggested dosage to have success is equal to 2.86 gr/kg/ day, a dosage is consistent with previously held studies. Even the therapeutic frequency is in line with the scientific evidence previously expressed. In addition, the evidence is given that with the doses and modalities expressed in the scenario the drug was successful and successful in the assessment.

Conclusions

The study for the first time tries to classify the costs of a clinical trial on the use of micafungin in neonates and young infants. The study provides an example of ways and items of expenses related to the clinical trial. The methodology used is applicable and can be used to compare future trials, thus identifying reference benchmarks (Minami et al., 2008; Schreyögg, 2008). The study through practical application seeks to identify the most correct method to avoid errors during the detection of clinical trials as evidenced by the study by Graves et al. (2002) through a correct application. The article also highlights the main cost items to be kept under control during the clinical trial phases. Moreover, given the incidence of candida infections in neonates and infants, the study increases the literature on the administration and testing of specific drugs for treatment and therapy. Future studies may address and compare the results obtained through the use of micafungin for the treatment of candida after having adopted the same approach and the same management relating to micro-costing.

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